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Dated 20 May 2003



Request for grant of a patent

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| | | | |
|---|---|---|--|
| 1. Your reference | PC25321 | | |
| 2. Patent application number (The Patent Office will fill in this part) | 17 SEP 2002 | 0221582.0 | |
| 3. Full name, address and postcode of the or of each applicant (underline all surnames) | PFIZER LIMITED Ramsgate Road, Sandwich, Kent, CT13 9NJ United Kingdom | | |
| 06892673001 Patents ADP number (if you know it) If the applicant is a corporate body, give the country/state of its incorporation | | | |
| 4. Title of the invention | METHOD OF TREATMENT | | |
| 5. Name of your agent (if you have one) | Dr. S. Cosway | | |
| "Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode) | UK Patent Department Ramsgate Road, Sandwich, Kent, CT13 9NJ United Kingdom | | |
| Patents ADP number (if you know it) | 08466302001 | | |
| 6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number | Country | Priority application number (if you know it) | Date of filing (day / month / year) |
| 7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application | Number of earlier application | Date of filing (day / month / year) | |
| 8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if: a) any applicant named in part 3 is not an inventor, or b) there is an inventor who is not named as an applicant, or c) any named applicant is a corporate body. See note (d)) | | | |

Patents Form 1/77

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| | |
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| Description | 8 |
| Claim(s) | 1 |
| Abstract | 0 DM |
| Drawing(s) | 0 |

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

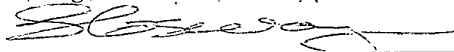
Request for substantive examination (*Patents Form 10/77*)

Any other documents
(please specify)

11.

I/We request the grant of a patent on the basis of this application.

Signature



Date

17 September 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Dr. S. Cosway

01304.643723

Warning

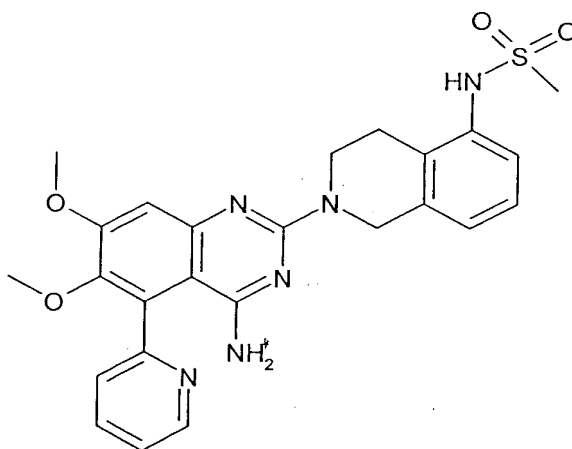
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Method of Treatment

This invention relates to a new use of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline
5 (disclosed as example 19 in International Patent Application Publication No. WO 98/30560), and its pharmaceutically acceptable derivatives. The mesylate salt is disclosed in International Patent Application Publication No. WO 01/64672 (e.g. Example 2). Both WO 98/30560 and WO 01/64672 are incorporated herein by reference. It is indicated in the treatment of Benign Prostatic Hyperplasia (BPH)
10 and has the following structure:



Lower urinary tract symptoms (LUTS) comprise three groups of symptoms, which
15 are irritative, obstructive and post micturition symptoms. Irritative symptoms comprise urgency, frequency and nocturia, which can be associated with: overactive bladder (with or without concomitant detrusor over activity); pelvic floor dysfunction; or chronic prostatitis.

20 Over Active Bladder (OAB) is defined as urgency, with or without urge incontinence, usually with frequency and nocturia [Abrams et al., Neurourology and Urodynamics 21:167-178 (2002)]. Prevalence of OAB in men and women is similar, with approximately 16% of the population of the USA suffering from the condition [Stewart et al, Prevalence of Overactive Bladder in the United States:

Results from the NOBLE Program; Abstract Presented at the 2nd International Consultation on Incontinence, July 2001, Paris, France].

5 Pelvic floor dysfunction (PFD) occurs when the muscles of the pelvic floor no longer relax properly during urination while the bladder contracts. The muscles may become irritated and often contract abnormally. PFD may result in irritative LUTS.

10 Chronic prostatitis is an inflammatory condition of the prostate, which may or may not be associated with uropathogenic bacteria detected by standard microbiological methodology. It is characterized by the presence of genitourinary pain or discomfort, often associated with irritative LUTS.

15 Overactive bladder may be suffered by individuals of any age, while pelvic floor dysfunction and prostatitis are conditions typically suffered by middle-aged men. Patients with any of these conditions are likely to experience irritative lower urinary tract symptoms, and often the eventual diagnosis is empirical.

20 Surprisingly it has been found that 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline is useful in the treatment of LUTS associated with: OAB (with or without concomitant detrusor over activity); pelvic floor dysfunction; or chronic prostatitis.

25 Thus, in accordance with the present invention, there is provided the use of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline, or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for the treatment of LUTS associated with: OAB (with or without concomitant detrusor over activity); pelvic floor dysfunction; or chronic prostatitis.

30

More preferably the LUTS is associated with pelvic floor dysfunction or chronic prostatitis.

More preferably the 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline is in the form of its mesylate salt.

The compound, or a pharmaceutically acceptable derivative thereof, can be administered alone or in any convenient pharmaceutical presentation. Oral administration is preferred. In the present indication, a suitable dosage of the compound, or of the active moiety in a pharmaceutically acceptable derivative thereof, is from about 0.01 to 10.0 mg/kg of body weight, and preferably about 0.05 to 1.0 mg/kg is suitable. Administration may be in single doses of from 1 to 10 times daily or preferably it may be in a controlled release formulation such as is disclosed in co-pending United Kingdom application No. 0124455.7 (see in particular examples 1 to 5). Administration may be p.r.n. for occasions when the patient may have limited access to facilities, e.g. during a long journey.

15 The invention further provides 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline, or a pharmaceutically acceptable derivative thereof, for use in the treatment of LUTS associated with: OAB (with or without concomitant detrusor over activity); pelvic floor dysfunction; or chronic prostatitis.

20

The invention further provides a method of treating LUTS associated with: OAB (with or without concomitant detrusor over activity); pelvic floor dysfunction; or chronic prostatitis, which comprises administering 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline, or 25 a pharmaceutically acceptable derivative thereof, to a patient in need of such treatment.

Examples 1-5**Tablet formulations of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline mesylate containing Methocel™ K4M**

- 5 The following table shows the ingredients for preparing five tablet formulations containing, respectively, 1, 3, 6, 9 and 12 mg of active ingredient, expressed as free base, according to co-pending United Kingdom application No. 0124455.7.

| Ingredient (mg) (reference to standard) | Ex 1 | Ex 2 | Ex 3 | Ex 4 | Ex 5 |
|--|----------------------|---------|---------|---------|---------|
| 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline mesylate (Pfizer) | 1.189 ⁽¹⁾ | 3.567 | 7.134 | 10.701 | 14.268 |
| HPMC (Methocel K4M, Ph.Eur) | 30.000 | 30.000 | 30.000 | 22.500 | 22.500 |
| Lactose Monohydrate (Ph.Eur) | 13.203 | 10.108 | 9.216 | 10.200 | 9.308 |
| Calcium Hydrogen Phosphate, Anhydrous (Ph.Eur) | 39.608 | 30.325 | 27.650 | 30.599 | 27.924 |
| Adipic Acid [DAB ⁽²⁾] | 15.000 | 25.000 | 25.000 | 25.000 | 25.000 |
| Magnesium Stearate (Ph.Eur) | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 |
| Tablet weight (mg) | 100.000 | 100.000 | 100.000 | 100.000 | 100.000 |

10 ⁽¹⁾ Equivalent to 1.0 mg 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline, in the form of its free base

⁽²⁾ DAB is the Deutsches Arzneibuch (German Pharmacopoeia)

Method

The adipic acid was first screened through a suitable screen (e.g. 500 micron). The lactose monohydrate, hydroxypropylmethyl cellulose, 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline mesylate, the screened adipic acid and calcium hydrogen phosphate, anhydrous were then added to a suitable blender (e.g. a tumble mixer) and blended. The blend was screened through a suitable screen (e.g. 500 micron) and reblended. About 50% of the lubricant (magnesium stearate) was screened, added to the blend and blended briefly.

10

The blend was roller compacted through a suitable roller compactor. The ribbon blend was then granulated, by screening through a suitable screen (e.g. 500 micron) and reblended. The remaining lubricant was screened, added to the blend and blended briefly.

15

The granules were then tableted using appropriate 6 mm tooling to give 6 mm standard round convex white tablets with no engraving, which were then dedusted.

20 **Example 6: In vivo study**

A 12-Week Study in men with lower urinary tract symptoms was undertaken in which the IPSS (International Prostate Symptom Score) was recorded at baseline during, and at the end of, double-blind treatment. The IPSS is composed of seven questions, each with potential responses of 0-5 on a Likert scale. These questions are grouped into two validated domains: the irritative domain (urgency, frequency and nocturia) and the obstructive domain (incomplete emptying, intermittency, weak stream and straining to begin). In addition, a bladder diary was completed by each subject to provide baseline incidence of individual symptoms, and subsequently to demonstrate change in incidence of these symptoms following double blind treatment. The average daily incidence of urgency, daytime micturition frequency and nocturia (the irritative symptoms) for

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each subject were derived from this diary. In this study, there were five treatment groups: 6mg fixed dose of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline, 6mg escalated to 12mg at Week 4 of the compound, and placebo. Controlled release formulations according to co-pending United Kingdom application No. 0124455.7 were used in each case.

For those subjects with irritative LUTS at baseline, improvement in these symptoms was confirmed in the compound 6mg fixed dose group and the 12mg dose escalation group, compared with the placebo treated group. In subjects with baseline IPSS irritative domain score ≥ 8 at baseline, improvement in this domain of the IPSS was similarly confirmed in both the compound 6mg fixed dose group and the 12mg dose escalation group.

The results of the study are illustrated in the figures below:

Figure 1. Urgency episodes per day – Week 12 change from baseline (≥ 1 episode per day at baseline)

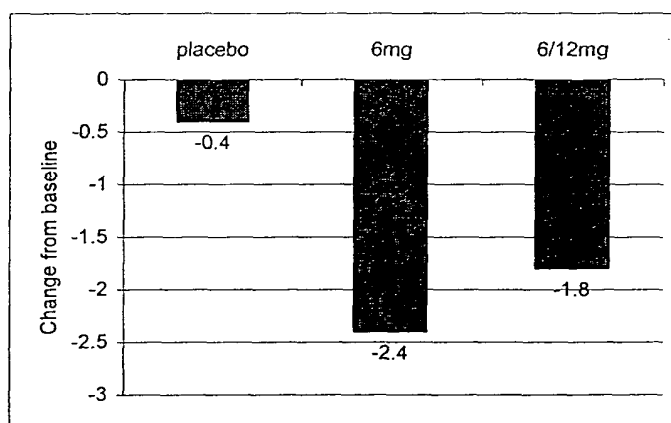
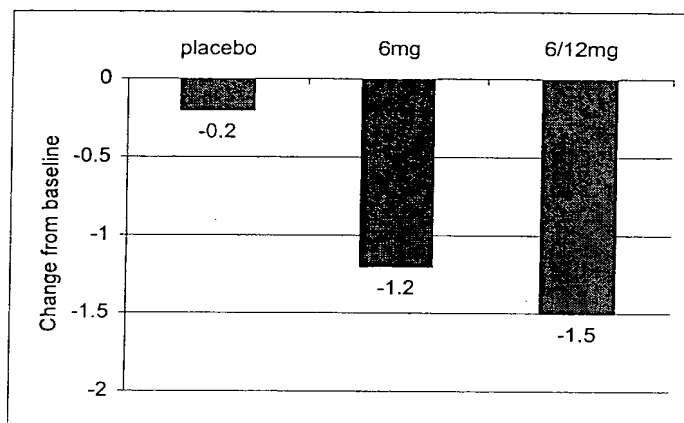


Figure 2. Daily frequency of micturition – Week 12 change from baseline (≥ 8 micturitions per day at baseline)



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Figure 3. Nocturia episodes per night – Week 12 change from baseline (≥ 2 episodes per night at baseline)

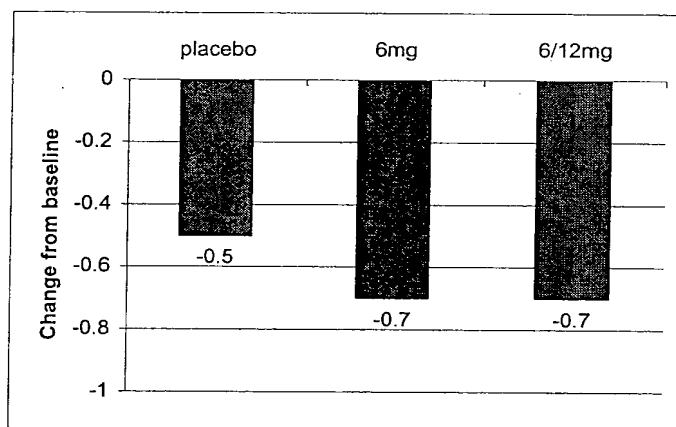
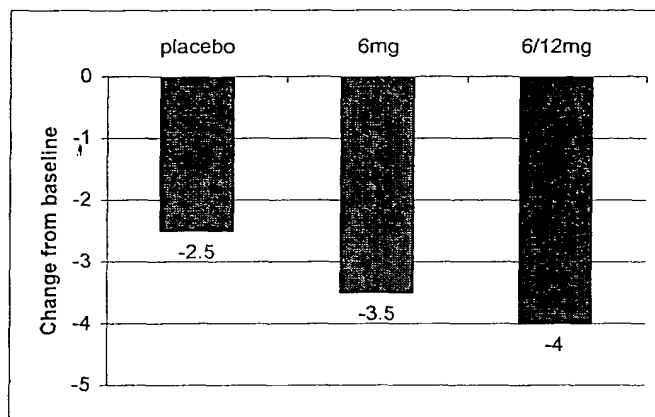


Figure 4. IPSS irritative domain – Week 12 change from baseline (score ≥ 8 at baseline)



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Conclusion:

The results show 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline produced a clinically significant
10 attenuation of irritative LUTS.

CLAIMS:

1. Use of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline, or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for the treatment of LUTS associated with: OAB (with or without concomitant detrusor overactivity); pelvic floor dysfunction; or chronic prostatitis.
2. 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline, or a pharmaceutically acceptable derivative thereof, for use in the treatment of LUTS associated with: OAB (with or without concomitant detrusor over activity); pelvic floor dysfunction; or chronic prostatitis.
3. A method of treating LUTS associated with: OAB (with or without concomitant detrusor over activity); pelvic floor dysfunction; or chronic prostatitis, comprising administering 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline, or a pharmaceutically acceptable derivative thereof, to a patient in need of such treatment.
4. A use or method as claimed in any one of claims 1 to 3, wherein the 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline is in the form of its mesylate salt.
5. A use or method as claimed in any one of claims 1 to 4, wherein the LUTS is associated with pelvic floor dysfunction or chronic prostatitis.

